NATIONAL PHARMACEUTICAL ALLIANCE

SUITE 222 . 421 KING STREET . ALEXANDRIA, VIRGINIA 22314 . (703) 836-8816 • FAX (703) 549-4749 . EMAIL NPA@EROLS COM

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

March 29, 1999

Docket No. 98D-0994

Gentlemen:

Enclosed are two copies of comments on the draft document "Guidance for Industry; BACPAC I: Intermediates in Drug Substance Synthesis - Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation" which closes March 31, 1999. The availability of the document appeared in the FR, Vol. 63, No. 229, page 65793-65794, November 30, 1998. These comments are made by the Technical Committee of the National Pharmaceutical Alliance.

Very truly yours,

Robert a. Jenssi for

Chris Sizemore
President

98D-0994

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COMMENTS BY THE NPA TECHNICAL COMMITTEE ON THE DRAFT GUIDANCE FOR INDUSTRY ON BACPAC I: INTERMEDIATES IN DRUG SUBSTANCES; BULK ACTIVES POSTAPPROVAL CHANGES: CHEMISTRY, MANUFACTURING AND CONTROLS DOCUMENTATION

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The NPA Technical Committee believes that this is a good first draft by FDA. However, there are several areas that need additional attention and/or reworking. Our comments will be in two parts: General Comments and Specific Comments.

GENERAL COMMENTS

1. The draft guidance provides no regulatory relief to DMF holders. All changes continue to require reporting through amendments via the respective drug applications. Thus, there are no changes that may be reported via annual report to the Master File even in cases where the change is within a single facility with no change in the synthetic pathway. The latter should be allowed and the application holders need not bother themselves or FDA headquarters with such a change.

2. The draft guidance introduces the concept of new impurities due to a change being controlled at the ICH O. 10/0 level in intermediates , a totally new concept beyond what ICH recommends. Footnote 7 on page 6 states that the ICH qualification thresholds for the drug substance are considered appropriate for evaluating impurity profiles in intermediates. Applying this ICH level at an intermediate stage when it may be reduced or eliminated in subsequent steps will only add work but little, if any, benefit.

3. There are at least eight places within the guidance that gives the advice to contact the appropriate reviewing division for guidance. These appear on pages 6,9, 11, 14 (twice), 15, 17, and 22 respectively. These should be completely eliminated or drastically reduced since it will lead to what now happens, namely, different advice from different reviewing divisions for the same circumstance. A guidance should stand on its own.

4. There are several places within the guidance where the statement is made that if either the impurity profile or physical properties are not equivalent in the drug substance, the change requires a prior approval supplement. When equivalence is not established the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered. We fail to see where the addition of an new impurity at or above the O. 10/0 level in the drug substance would affect bioequivalence and do not think this would ever be necessary.

SPECIFIC COMMENTS

1. Under II. General Considerations (lines 57) appears the following "This guidance is limited to changes made up to and *including the final intermediate* _____." (emphasis added) This is confusing in view of footnote 4 on page 2 which states that "Changes to the final intermediate and manufacturing changes after the final intermediate will be covered in the forthcoming

BACPAC II guidance." If BACPAC II will start with the final intermediate, BACPAC I should not include it.

Also under this section is the sentence (lines 73-76) "If the method of manufacture is described in a master file, then documentation of the modification should be filed as an amendment(s) to the master file _____." We recommend that immediately after the phrase "to the master file" be added "or in the annual report as appropriate".

2. Under III. Assessment of Change (lines81 -91) all deal with the central tenet of the draft guidance that a given change in the drug substance manufacturing process can be adequately assessed by comparing pre- and postchange material. This statement should apply primarily to the drug substance and not to intermediates. This section also states that "When equivalence cannot be demonstrated, a prior approval supplement should be submitted by the applicant(s) and the need for qualification of impurities, demonstration of bioequivalence, and assessment of stability should be considered" seems excessive. If the new process (step modification, etc.) does introduce a new impurity at or above the O. 10/0 level why would that require bio? And what are the chances that it would affect physical properties?

3. Under A. Equivalence of Impurity Profiles (lines 105-106) is mentioned impurity profile evaluation "in isolated intermediates immediately following the processing step in which any manufacturing modification is made". This either presumes that the intermediate impurity profile is previously known or that it must be determined at this stage both pre- and postchange. This appears to be the addition of unnecessary effort since any new impurity could be potentially removed in any subsequent steps on the path to the drug substance. The latter is partially recognized (lines 113- 117) where it may not be possible to establish equivalence at an intermediate stage but only in the cases where analytical methods may not be available or cannot be developed or historical data may not exist. Then testing maybe carried out on the drug substance itself. The problem with this approach is that most isolated intermediates will not have historical data on total impurities with the possible exception of the final intermediate. Since lines 134-136 recognize that "further reduction of impurity levels will frequently occur in the subsequent step or steps prior to drug substance formation", this section should be modified to allow a firm to go to the finished drug substance before determining if any change in the impurity profile of the latter has occurred. Pilot studies would inform the firm if this was feasible and practical.

4. Footnote 7 on page 6 states that "although the ICH guidance is intended for the registration applications of new drug substances, the qualification thresholds established are appropriate for evaluating impurity profiles for BACPAC I." We contend that it is not appropriate for BACPAC I since the 0.1 % qualification threshold is for the substance actually received by patients and whose level could have an impact on patients. However, patients are not administered intermediates and additional impurities are not qualified in intermediates but rather in drug substances. It is what impurity levels exist in the drug substance, not intermediates, that matters.

5. Under Site Changes (lines261 -265) for a site change that does not involve the final intermediate, we recommend that it be reported in an annual report to a DMF and not to an

application,

A changes being effected supplement is required if the site change involves the final intermediate (lines 266-267) but the final intermediate is to be covered in BACPAC II so why is it mentioned herein?

6. Under Scale Changes (lines 307-308) we recommend that the filing documentation be an annual report in the DMF, not in the respective applications.

7. Under C. Manufacturing Process Changes (lines 415-416) three batches are required for a changed process. May this be pilot batches or must they be production batches? Also under this section (lines 422-427) the concept of ICH solvent limits to intermediates when a new solvent is used in the synthetic process does not seem to be applied. If the solvent is below the ICH Q3C Option 1 limit in the drug substance, no testing would be required on the drug substance for the new solvent. Unlike the formation of a new impurity in an intermediate, the drafters of this guidance recognize that it may simply be easier for a firm to test the drug substance for the new solvent and not the intermediate. The same option should be available for impurities and not only under special circumstances (lines 112-1 17).

Glossary of Terms:

Drug Substance: The definition as written doesn't seem to include a prodrug. With the latter, the actual drug substance may be the final intermediate in the synthesis of the prodrug. The latter may not have any pharmacological activity.

Historical Data: How many firms will have 10 recent batches representative of the established process. We recommend that this number be reduced to five.

Starting Material: The definition states that the SM is incorporated as an element into the structure of an intermediate and/or drug substance. This definition should be expanded to more clearly state that a SM may only be partially incorporated into the structure of an intermediate or drug substance.